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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,278	04/08/2004	Thomas W. Leonard	9448-51	1153

20792 7590 03/02/2009
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EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
03/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,278	LEONARD, THOMAS W.	
	Examiner	Art Unit	
	SAHAR JAVANMARD	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-16,19-23 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-16, 19-23 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 8/29/08. Claim(s) 10-16, 19-23 and 29 are pending and are examined herein.

Response to Arguments

Applicants presented no arguments over the Obvious Double Patenting rejection of claims 10-16 as being unpatentable over claims 1-7 of Application No. 10/678,828. Because said copending application is now a patent, the provisional Obvious Double Patenting rejection of Application No. 10/678,828 is hereby withdrawn and a new nonstatutory obviousness-type double patenting rejection is set forth below.

Applicants presented no arguments over the Obvious Double Patenting rejection of claim 1 as being unpatentable over claims 1and 6 of copending Application No.10/356,242. The rejection is maintained for the reasons of record but modified in view of Applicant's cancellation of claims 17, 18, 24, and 25.

Applicant's arguments with respect to the 103(a) rejection of claims 10-26 and 29 as unpatentable over Pickar (2001/0034340) in view of Labrie (5798347), Coulson (4381298), Prestwood et al. (The Effect of Low Dose Micronized 17-□-Estradiol on Bone Turnover, Sex Hormone Levels, and Side Effects in Older Women: A Randomized, Double Blind, Placebo-Controlled Study, *Journal of*

Clinical Endocrinology and Metabolism, Vol. 85, No.12) and Utian et al. (Efficacy and safety of low, standard, and high dosages of an estradiol transdermal system (Esclim) compared with placebo on vasomotor symptoms in highly symptomatic menopausal patients, *American Journal Of Obstet Gynecol* 1999 Jul;181(1):71-9) has been fully considered but is not persuasive.

Applicant argues that none of the cited references teach or suggest the recitation of "said second dose comprising a lower dosage of said therapeutic amount of an estrogenic compound than said first dose" as in Claim 10." In response, Examiner points to the teachings of Pickar et al. in which it is stated that "the dosage of a patient may need to be adjusted (either up or down), to achieve the desired effect during the middle of a treatment period. [0022]." Therefore, the reference teaches it is well within the purview of a skilled artisan to adjust the dosage of an estrogenic compound to achieve the desired effect during the middle of a treatment period.

Further, the Applicant argues that Prestwood et al. and Utian et al. "describe a minimum dosage of estrogen for specific symptoms; however, neither references suggest or teach a treatment which starts out a high dose of estrogenic compound and then gradually lowering the dose as claimed in Claim 10." Additionally Applicant argues that there is no motivation in the cited references to modify or combine references teachings in order to achieve the claimed invention. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art

to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Pickar et al. teaches "the dosage of a patient may need to be adjusted (either up or down), to achieve the desired effect during the middle of a treatment period. [0022]." Further, Prestwood et al. teaches that it was found that breast tenderness, bleeding, and endometrial changes were significantly less frequent in the 0.25 mg/day and placebo groups compared with the higher dose groups; and Utian et al. teaches the main reason for changing to a lower dosage in ERT is to reduce estrogen side effects, especially genital bleeding and breast pain. It is therefore necessary to obtain a balance between relief of symptoms and the risk of adverse effects. The combination of the teachings of Pickar et al., Prestwood et al. al., and Utian et al. provide motivation as to why a person of ordinary skill in the art would lower the second dosage of a drug. The skilled artisan would have had reasonable expectation of successfully producing the desired effect by adjusting the dosage.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one

examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10-16 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 7427609 B2 to Leonard et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims encompass overlapping inventions, in that a method of treating vasomotor symptoms comprises administering a therapeutic amount of an estrogenic compound, and a therapeutic amount of progestational compound.

Claim 1 is also provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1and 6 of copending Application No.10/356,242. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims encompass overlapping inventions, in that a method of treating vasomotor

symptoms comprises administering a therapeutic amount of an estrogenic compound, and a therapeutic amount of progestational compound.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10-16, 19-23 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pickar (2001/0034340) in view of Labrie (5798347), Coulson (4381298), Prestwood et al. (The Effect of Low Dose Micronized 17-□-Estradiol on Bone Turnover, Sex Hormone Levels, and Side Effects in Older Women: A Randomized, Double Blind, Placebo-Controlled Study, *Journal of Clinical Endocrinology and Metabolism*, Vol. 85, No.12) and Utian et al. (Efficacy and safety of low, standard, and high dosages of an estradiol transdermal system (Esclim) compared with placebo on vasomotor symptoms in highly symptomatic menopausal patients, *American Journal Of Obstet Gynecol* 1999 Jul;181(1):71-9).

Pickar teaches a composition comprising preferably conjugated estrogens such as PREMARIN (conjugated equine estrogens, USP) and CENESTIN (synthetic conjugated estrogens, A), and medroxyprogesterone acetate (androgen and progestin) as an estrogen replacement therapy. PREMARIN (conjugated estrogens tablets, USP) for oral administration contains a mixture of estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended. A mixture of sodium estrone sulfate and sodium equilin sulfate, and at least the following 8 concomitant components, also as sodium sulfate conjugates: 17- α-dihydroequilin, 17-α-estradiol,.δ-8,9-dehydroestrone, 17-β-dihydroequilin, 17-β- estradiol, equilenin, 17-α-dihydroequilenin, and 17-β-dihydroequilenin. PREMARIN is indicated in the treatment of moderate to severe vasomotor symptoms associated with the menopause. It is preferred that the dosage of PREMARIN is about 0.625 mg per

day or less, and is more preferred that the dosage of PREMARIN is either about 0.45 mg per day or about 0.30 mg per day [0016] and a daily dose of medroxyprogesterone acetate in the amount of about 1.5 mg. The components of the combination are preferably administered at the same time; either as a unitary dosage form containing both components, or as separate dosage units; the components of the combination can be administered at different times during the day, provided that the desired daily dosage is achieved ([0011]).

The term "continuous and uninterrupted" means that there is no break in the treatment regimen, during the treatment period. Thus, "continuous, uninterrupted administration" of a combination, means that the combination is administered at least once daily during the entire treatment period. It is expected that the treatment period for the combination of conjugated estrogens and MPA will be for at least 30 days, preferably 120 days, and most preferably as long term treatment, and possibly indefinite, as one of the primary reasons for administering combinations of conjugated estrogens and MPA is to treat or inhibit menopausal or postmenopausal disorders. Treatment periods also may vary depending on the symptoms to be treated. For example, for the treatment of vasomotor symptoms, it is preferred that the treatment may last from one month to several years, depending on the severity and duration of the symptoms [0020]. One aspect of this invention also covers situations in which a fixed daily dosage of the conjugated estrogens plus MPA combination is not given every day during the treatment period. For example, the dosage of a patient may need to be adjusted (either up or down), to achieve the desired effect during the middle of a

treatment period [0022].

As these estrogens decline during the time preceding (perimenopause) and following the menopause (postmenopause), various physiological changes may result, including vulvar and vaginal atrophy causing vaginal dryness, pruritus and dyspareunia, and vasomotor instability manifested as hot flushes. Other menopausal disturbances may include depression, insomnia, and nervousness. Estrogen replacement therapy (ERT) is beneficial for symptomatic relief of hot flushes and genital atrophy and for prevention of postmenopausal osteoporosis.

Labrie is solely incorporated to show that medroxyprogesterone acetate is a progestin.

Coulson is solely incorporated to show that medroxyprogesterone acetate is an androgen.

Pickar fails to specifically teach the second dose of an estrogenic compound is administered after therapy of the vasomotor symptoms has been effectively established, wherein "the second dose of an estrogenic compound is administered between 2 weeks and 12 weeks after the first dose of an estrogenic compound," "the second dose of an estrogenic compound is administered between 4 weeks and 8 weeks after the first dose of an estrogenic compound," "the first predetermined time period for said first dose of an estrogenic compound is at least twelve weeks before the administration of said second dose of an estrogenic compound," or "the first predetermined time period for said first dose of an estrogenic compound is at least four to eight weeks before the administration of said second dose of an estrogenic compound."

Prestwood et al. teaches the measure of serum and urinary biochemical markers of bone resorption and formation at baseline 6 and 12 weeks on treatment. Also, Prestwood et al. measured serum estradiol, estrone, and sex hormone-binding globulin levels at baseline, 12 weeks on treatment, and 12 weeks posttreatment. It was found that breast tenderness, bleeding, and endometrial changes were significantly less frequent in the 0.25 mg/day and placebo groups compared with the higher dose groups.

Additionally, Utian et al. teaches the main reason for changing to a lower dosage in ERT is to reduce estrogen side effects, especially genital bleeding and breast pain. It is therefore necessary to obtain a balance between relief of symptoms and the risk of adverse effects.

It would have been obvious to a skilled artisan to treat vasomotor symptoms comprising a first dose of a therapeutic amount of an estrogenic compound to a subject; and administering a second dose of a therapeutic amount of an estrogenic compound at a later time period to the subject, said second dose comprising a lower dosage of said therapeutic amount of an estrogenic compound than said first dose to produce the required effect, i.e., to treat vasomotor symptoms. The motivation to administer the dosage in a first and lower second dosage or even a lower third dosage is because (1) Prestwood et al. teaches it was found that breast tenderness, bleeding, and endometrial changes were significantly less frequent in the 0.25 mg/day and placebo groups compared with the higher dose groups (2) Utian et al. teaches the main reason for changing to a lower dosage in ERT is to reduce estrogen side effects,

especially genital bleeding and breast pain. It is therefore necessary to obtain a balance between relief of symptoms and the risk of adverse effects and (3) Pickar teaches the dosage of a patient may need to be adjusted (either up or down), to achieve the desired effect during the middle of a treatment period. Hence a skilled artisan would have had reasonable expectation of successfully producing the desired effect by adjusting the dosage.

Conclusion

Claims 10-16, 19-23 and 29 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the

statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAHAR JAVANMARD whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/S. J./

Examiner, Art Unit 1617

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617